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ORIGINAL RESEARCH

The Effect of Prenatal Marijuana Exposure on White Matter Microstructure and Cortical Morphology During Late Childhood

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ABSTRACT

BACKGROUND AND PURPOSE: Marijuana consumption by pregnant women has been steadily increasing over the past decades. Even though many pregnant women perceive marijuana consumption as safe during pregnancy it has been previously linked to poor maternal and neonatal outcomes. The specific long lasting neurodevelopmental alterations caused by prenatal marijuana exposure in children are still underexplored. Thus, this study aims to determine the effect of prenatal marijuana exposure on brain neurodevelopment at late childhood.

MATERIALS AND METHODS: This cross-sectional study investigated the relationship between prenatal marijuana exposure and neuroimaging markers of brain health. Data was obtained from the Adolescent Brain Cognitive Development study, a large, demographically diverse, multicenter cohort. The study included 1,085 children, 418 of whom were prenatally exposed to marijuana and 667 matched controls with no prenatal exposure, with a mean age of 9.9 (SD = 0.6) years in both groups.

RESULTS: We found that prenatal exposure to marijuana is associated with brain alterations in white matter tracts and cortical regions essential for goal directed behaviors, including motivation, cognitive skills for achieving specific objectives, and emotional processing. Direct group comparisons revealed significantly reduced white matter integrity in prenatally exposed children, with an overall reduction in lower fractional anisotropy and neurite density, and higher mean diffusivity and radial diffusivity. Furthermore, mixed linear model regressions revealed that prenatal marijuana exposure was significantly associated with decreased white matter microstructure, predominantly in the superior corticostriate tract and corticostriate projections via the external capsule to the superior parietal and frontal cortices and with reduced cortical surface area on the left hemisphere parahippocampal and right hemisphere postcentral gyrus.

CONCLUSIONS: Overall, our findings suggest that prenatal exposure to marijuana may have long lasting alterations in children brain neurodevelopment. These alterations may impair critical skills needed as children grow into adolescence.

ABBREVIATIONS: WM = white matter; DTI = Diffusion Tensor Imaging; FA = Fractional Anisotropy; MD = Mean Diffusivity; RD = Radial Diffusivity; ND = Neurite Density; sMRI = structural MRI; ABCD = Adolescent Brain Cognitive Development

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SUMMARY SECTION

PREVIOUS LITERATURE: Previous studies have linked prenatal marijuana exposure to behavioral issues in early childhood. However, most prior studies have relied only on behavioral assessments rather than utilizing direct neuroimaging metrics to analyze the impact of prenatal marijuana exposure on children neurodevelopment. Our study builds on previous literature by using multimodal MRI neuroimaging techniques to assess the long-term brain structural alterations caused by prenatal exposure to marijuana.

KEY FINDINGS: Prenatal marijuana exposure was associated with reduced white matter microstructural integrity, with observed alterations mainly localizing to the corticostriate circuitry. Exposed children also exhibited reduced cortical surface area in the left parahippocampal and right postcentral gyri, regions involved in goal-directed behavior, sensory processing, and emotional regulation.

KNOWLEDGE ADVANCEMENT: This study provides the largest neuroimaging-based analysis of prenatal marijuana exposure effects in late childhood, utilizing a diverse, nationally representative cohort. By integrating multimodal imaging techniques, our findings highlight significant brain alterations that may underlie behavioral risks in those children prenatally exposed to marijuana.

INTRODUCTION

Marijuana consumption by pregnant women in the United States has been steadily increasing over the past two decades [1]. Among pregnant women, the past-month marijuana consumption increased 62% from 2002 through 2014 [1]. The steady increase in marijuana consumption by pregnant women may be partially related to an increase in marijuana consumption by pregnant woman following the legalization of recreational cannabis in various states of the country [2]. In addition, studies have found an increased perception of safety regarding marijuana

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consumption during pregnancy [3]. Pregnant women report using marijuana to manage mood and physical symptoms associated with pregnancy, with many considering it a potentially safer alternative compared to regular prescription medications [3]. However, prenatal marijuana exposure has also been associated with adverse maternal and neonatal health outcomes [4, 5]. In addition, studies have also found long lasting associations between prenatal marijuana exposure and child behavior development, with problems observed at late childhood, such as increased hyperactivity, inattention symptoms, and increased delinquency [6].

Previous neuroimaging studies have explored the effects of prenatal marijuana exposure on children's brain development and neurocognitive outcomes. A large-scale analysis study found that prenatal marijuana exposure was associated with increased attention problems and externalizing behaviors in young adolescents [7]. In addition, studies have examined structural brain differences in children exposed prenatally to marijuana and found that, prenatal exposure is linked to cortical morphology alterations in the frontal regions of the brain [8]. Despite these insights, significant gaps in knowledge remain regarding the long-term impact of prenatal exposure to marijuana on brain white matter microstructure and cortical morphology, particularly at late childhood. While previous studies have identified behavioral alterations, the underlying neurobiological and microstructural mechanisms remain unclear.

Diffusion Tensor Imaging (DTI) provides a valuable tool for addressing these knowledge gaps by tracking the movement of water molecules within brain tissue along white matter (WM) axonal pathways, enabling the calculation of key diffusion metrics, such as fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) [9, 10]. Moreover, by employing multi-compartmental modeling from multi-shell diffusion MRI we can calculate restriction spectrum metrics such as neurite density (ND). All of these diffusion metrics provide detailed information about the organization and microstructural integrity of brain WM, especially in relation to childhood neurodevelopment [11, 12]. On the other hand, structural MRI (sMRI) may be used to obtain quantitative measures of the cortical surface area of the brain. Cortical surface area, a measure of the total area of the brain's cortex serves as an important metric for assessing neurocognitive development [13]. By integrating DTI and sMRI analyses, our study can offer a comprehensive understanding of how prenatal exposure to marijuana affects neuroimaging metrics of brain health.

Even though patterns of behavioral problems have already been observed on children who were prenatally exposed to marijuana, the specific long lasting neurodevelopmental brain alterations which may be caused by prenatal exposure to marijuana are underexplored. In addition, most of the studies which have explored the long-lasting impacts of prenatal marijuana exposure on children neurodevelopment rely mainly on the use of child behavior checklists and neurobehavioral assessments [14] . By using advanced neuroimaging techniques, we can determine and quantify the long-lasting impact of prenatal marijuana exposure at late childhood on brain neurodevelopment. In our study, we utilized data from the Adolescent Brain Cognitive Development (ABCD) study to investigate the effects of prenatal marijuana exposure on neurodevelopment within a large, racially and ethnically diverse sample of children. The ABCD study recruited over 11,800 children from 21 sites across the United States. Children ages 9–10 were selected from different sites across the country to capture a broad socio-demographic range cohort of children for this nationally representative cohort. [15, 16]. We analyzed the effect of prenatal marijuana exposure on MRI diffusion metrics of WM microstructural integrity and cortical morphology surface area metrics. The objective of this study was to assess whether prenatal marijuana exposure is associated with long-term alterations in WM microstructure and cortical morphology. By utilizing advanced neuroimaging techniques, we aim to provide a more comprehensive understanding of the neurobiological impact of prenatal marijuana exposure.

MATERIALS AND METHODS

Adolescent Brain Cognitive Development Database

The Adolescent Brain Cognitive Development (ABCD) study is a large, longitudinal research project designed to investigate brain development and health in children. This study analyzes 11868 children, recruited from 21 sites across the United States, starting at ages 9 to 10 at baseline. The study collects a wide range of data, including neuroimaging metrics, cognitive assessments, genetic information, and environmental factors, to understand how various factors may affect brain development, behavior, and overall health. It is the largest long-term study of brain development and child health in the U.S.

This cross-sectional study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. We used the ABCD study to obtain all the demographic, neuroimaging, and prenatal drug exposure data of 11868 subjects (release 5.1). The subjects included in our analysis were between the ages of 9 and 10 years and were recruited from September 2016 to August 2018. All data obtained was retrospectively analyzed. The ABCD study recruited participants through 21 research centers across the United States. Each research center received institutional review board (IRB) approval from its respective institution, with additional central IRB approval obtained from the University of California, San Diego. Informed consent was also obtained from both parents and participants. Participants in the ABCD study were excluded if they lacked proficiency in English, were unable to tolerate a baseline MRI scan, had severe medical, neurological, or sensory impairments, or had intellectual limitations [17, 18].

Inclusion and Exclusion Standards for Study Analysis

Only participants who had complete neuroimaging data, prenatal drug exposure data and complete demographic information (age, sex, weight, height, handedness, race, parental education, and parental income) were included in our study. Participants with likely biologically implausible BMI z-scores (<-4 or >8) as established by the CDC growth charts [19] were excluded from our analysis. Those participants with any noted abnormality or pathology as revealed by neuroimaging studies, participants whose scans yielded poor imaging quality, or those with a history of traumatic brain injury, were also excluded from our study. Lastly, to minimize demographic differences between children prenatally exposed to marijuana and control children who were not prenatally exposed to marijuana, the final dataset was matched by race, parental income, parental education, and current BMI z-scores. To create a well-matched control group, we estimated propensity scores using logistic regression, modeling the likelihood of prenatal marijuana exposure based on relevant covariates, including BMI z-score, race, parental education, household income, and K-SADS diagnosis. We then divided the dataset into two groups, children who

were prenatally exposed to marijuana and children who were not exposed. To achieve optimal matching, we employed a nearest-neighbor approach using Euclidean distance on propensity scores, pairing each exposed individual with the closest non-exposed counterpart.

Demographic Characteristics

The ethnicity/race of all participants included in our study was classified into five distinct categories: White, Black, Asian, Hispanic, and multiracial or other. The parental education level was determined based on the highest educational level of either parent. In total, parental education was initially recorded in 21 distinct levels, ranging from primary school to postgraduate degrees. For clarity and analysis, these levels were grouped into five broader categories: below high school graduate, High School or GED, some college or associate degree, bachelor's degree, and postgraduate education. Similarly, parental income was divided into 10 categories, ranging from less than $5,000 to more than $200,000. Participant handedness was categorized into three groups: right-handed, left-handed, and mixed handed. Participants classified as mixed handed included those who did not exhibit a consistent preference for either hand across various tasks or reported using both hands interchangeably. Psychiatric diagnoses for participants in this study were determined using the K-SADS (Kiddie Schedule for Affective Disorders and Schizophrenia), a structured, diagnostic tool administered as part of the ABCD Study. The primary informants were caregivers, with some input from child self-reports. K-SADS applies a standardized, algorithm-based approach to assess psychiatric conditions based on DSM-5 criteria. Participants were classified as having a disorder if they met the full symptom and impairment criteria as defined by DSM-5.

Prenatal Marijuana Exposure

The ABCD study determined prenatal marijuana exposure through retrospective maternal reports. Children were classified as prenatally exposed to marijuana if their mothers reported using marijuana at any time during pregnancy, whether before or after pregnancy awareness [20]. In contrast, control children were defined as those whose mothers reported no marijuana use throughout their entire pregnancy, both before and after pregnancy confirmation.

Neuroimaging metrics

To ensure consistency, the ABCD study utilized 3 Tesla scanners across all imaging sites, with acquisition protocols standardized. Scanners from Siemens, Philips, and GE were used to acquire structural, diffusion, and functional MRI data. Once captured, the images were corrected for motion and distortion and aligned to a standardized reference space. Neuroradiologists examined the scans for incidental or pathological findings and referred subjects for clinical evaluation as necessary. Diffusion MRIs were performed using sequences with varying b-values and directions. Processing of these images involved several correction steps, including adjustments for eddy currents, head motion and rotation, B0 distortion, and gradient nonlinearity. After applying these corrections, the T2-weighted B0 images were aligned with T1-weighted structural images and converted to a 1.7-mm isotropic standard space. Several diffusion metrics, including fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity, were calculated. Neurite density was also measured using restriction spectrum imaging. The AtlasTrack software was subsequently used to segment and analyze diffusion tensor imaging (DTI) and restriction spectrum imaging (RSI) metrics across 35 WM tracts. Structural MRI data was obtained by segmenting the cortical surface from T1-weighted scans and aligning them with a surface-based atlas through nonlinear registration using FreeSurfer software, version 5.3.0. The Desikan-Killiany atlas was applied to identify surface areas across 68 cortical regions. Additionally, intracranial volumes were measured using the ASEG atlas. A complete list of all white matter tracts and cortical surface area regions analyzed is available on Supplementary Table 1.

Statistical Analysis

To establish the potential association of prenatal marijuana exposure with average diffusion metrics of each WM tract we utilized mixed linear models. As shown in Figure 1, only participants who had complete neuroimaging data, prenatal drug exposure data and complete demographic information (age, sex, weight, height, handedness, race, parental education, and parental income) were included in our statistical analysis. From a total of 11868 participants in the ABCD study, 1331 were excluded due to no available information, 2505 were excluded due to not having neuroimaging data, 31 were excluded due to having unlikely BMI's, 307 were excluded due to having traumatic brain injuries, and finally 6609 were excluded in order to match the demographic variables of the control group with those subjects prenatally exposed to marijuana. Current BMI z-scores for all subjects were calculated using the 'growthcleanr' package in R, based on the age and sex specific reference values provided by the World Health Organization. The WHO Growth Reference defines BMI categories based on standard deviations (z-scores) from the median BMI-for-age, where values below -3 SD indicate severe thinness, below -2 indicate thinness, -2 to 1 is normal, above than 1 indicate overweight, and above than 2 SD indicate obesity [21]. All demographic baseline characteristics of the study participants (Table 1) were compared based on children marijuana exposure status using appropriate statistical tests. Continuous variables (e.g., Age, BMI z-score) were compared within exposed and control groups by applying independent t-tests to assess differences in means between groups. Categorical variables (e.g., Sex, Race/Ethnicity, Parental Education, Handedness, and Parental Income) were compared within exposed and control groups using chi-square tests to determine group differences.

To examine baseline neurodevelopmental differences between those children prenatally exposed to marijuana and those who were not exposed, we first performed independent t-tests in R, version 4.4.3 to compare DTI metrics and cortical surface area metrics between children prenatally exposed to marijuana and non-exposed controls. False Discovery Rate (FDR) correction was applied to adjust for multiple comparisons. We then used the python library "statsmodels" in order to run our mixed linear model analyses. The average diffusion metrics for each of the WM tracts analyzed were dependent variables, and the children prenatal marijuana exposure status (yes or no) along with all other biological and demographic covariates were independent predictors in each one of our models. The same process was used to establish the relationship between prenatal marijuana exposure with cortical surface area. The following covariates were included in all mixed linear model analyses: the subjects age at time of scan, current BMI-z score, handedness, race, sex, presence of any K-SADS diagnosed mental health disorders, and cranial volume. Both the highest parental level of education and the combined parental

income were adjusted for as random effects in our analyses. Significant p-values were set at 0.05 and all p-values were adjusted for multiple comparisons using the Benjamini-Hochberg method [22]. Data visualization for was performed in Python, version 3.9.21. Libraries used for data visualization included nilearn, nilabel, pandas, matplotlib, seaborn, and numpy.

RESULTS

Participants Summary

Figure 1 shows the inclusion flowchart for subjects from the ABCD study dataset. Our analysis included a total of 1,085 children with complete demographic, neuroimaging, and prenatal drug exposure data. A total of 418 children who were prenatally exposed to marijuana and 667 matched controls who were not prenatally exposed to marijuana were included in our analysis. Both groups had a mean (standard deviation, SD) age of 9.9 (0.6) years. The group of children prenatally exposed to marijuana consisted of 196 males (46.9%) and 222 females (53.1%), whereas the control group had 346 males (51.9%) and 321 females (48.1%). The proportion of children identifying as White (41.6% vs. 42.9%), Black (28.9% vs. 23.2%), Hispanic (19.9% vs. 24.0%), Asian (0.95% vs. 1.35%), and Multiracial/Other (8.6% vs. 8.6%) was comparable between the group of children prenatally exposed to marijuana and the control group. Table 1 summarizes the demographic characteristics of all the subjects included in our analysis (n=1085).

Comparison of Neuroimaging Metrics Between Prenatally Marijuana Exposed Children and Non-Exposed Controls

Prior to investigating associations between prenatal marijuana exposure and neuroimaging metrics of brain health, we compared DTI metrics and cortical surface area metrics between exposed and non-exposed children. Overall, our results showed lower fractional anisotropy and neurite density, and higher mean and radial diffusivity among exposed children. Lastly, exposed children had significantly decreased cortical surface area in left hemisphere parahippocampal, and right hemisphere postcentral gyrus compared to non-exposed children. Supplementary Table 2 lists all DTI and cortical surface area metrics where significant differences were observed between prenatally marijuana exposed children and non-exposed controls.

Effects of Prenatal Marijuana Exposure on Fractional Anisotropy

Analysis of WM diffusion metrics showed that prenatal exposure to marijuana correlated with significantly lower mean FA in multiple WM tracts. This was most prominently observed in the superior corticostriate (Left: $\beta = -0.005$, P= 0.005; Right: $\beta = -0.006$, P= 0.02) and the corticostriate projections via the external capsule to the superior parietal cortex (Left: $\beta = -0.006$, P= 0.01; Right: $\beta = -0.006$, P= 0.01) (Figure 2). Supplemental Table 3 list all WM tracts with significant associations between prenatal marijuana exposure and FA.

Effects of Prenatal Marijuana Exposure on Mean Diffusivity

Significant positive association with WM diffusion metrics of MD were observed in those children prenatally exposed to marijuana, predominantly in the superior corticostriate (Left: $\beta = 0.003$, P= 0.009; Right: $\beta = 0.003$, P= 0.01) and the corticostriate projections via the external capsule to the superior parietal cortex (Left: $\beta = 0.003$, P= 0.01; Right: $\beta = 0.003$, P= 0.01) (Figure 2). Supplemental Table 4 list all WM tracts with significant associations between prenatal marijuana exposure and MD.

Effects of Prenatal Marijuana Exposure on Radial Diffusivity

Children prenatally exposed to marijuana showed significant positive associations with WM diffusion metrics of RD, primarily at the forceps major ($\beta = 0.004$, P= 0.04), the superior corticostriate (Left: $\beta = 0.004$, P= < 0.001; Right: $\beta = 0.004$, P= < 0.001), the corticostriate projections via the external capsule to the superior parietal cortex (Left: $\beta = 0.004$, P= < 0.001; Right: $\beta = 0.004$, P= < 0.001), and the corticostriate projections via the external capsule to the superior frontal cortex (Left: $\beta = 0.004$, P= < 0.001; Right: $\beta = 0.003$, P= 0.004) (Figure 2). Supplemental Table 5 list all WM tracts with significant associations between prenatal marijuana exposure and RD.

Effects of Prenatal Marijuana Exposure on Neurite Density

Analysis of WM diffusion metrics showed that prenatal exposure to marijuana correlated with significantly lower mean ND in multiple WM tracts. This was most prominently observed in the superior corticostriate (Left: $\beta = -0.005$, P= < 0.001; Right: $\beta = -0.005$, P= 0.005) and the corticostriate projections via the external capsule to the superior parietal cortex (Left: $\beta = -0.005$, P= 0.001; Right: $\beta = -0.006$, P= 0.003) (Figure 2). Supplemental Table 6 list all WM tracts with significant associations between prenatal marijuana exposure and ND.

Effects of Prenatal Marijuana Exposure on Cortical Surface Area

Children that were prenatally exposed to marijuana showed significant cortical surface area reductions in the left hemisphere parahippocampal region ($\beta = -14.7$, P= 0.007) and the right hemisphere postcentral region ($\beta = -73.4$, P= 0.04) (Figure 3). Supplemental Table 7 list the regions exhibiting significant associations between prenatal marijuana exposure and cortical surface area.

DISCUSSION

Our study found that prenatal marijuana exposure is associated with alterations in WM microstructure and cortical morphology in children. These findings remained significant even after adjusting for confounding factors, suggesting that prenatal marijuana exposure may have long-lasting neurodevelopmental consequences. Our analysis of group comparisons revealed that children who were prenatally exposed to marijuana exhibited significantly lower FA and ND, as well as increased MD and RD, compared to non-exposed children. These alterations suggest decreased WM integrity, axonal organization, and myelination processes in those children who were prenatally exposed to marijuana. Additionally, cortical surface area was also reduced in exposed children, indicating broader structural differences that may impact cognitive and behavioral outcomes.

In addition, our regression analysis examined whether prenatal marijuana exposure remained a significant predictor of WM microstructural integrity after adjusting for confounders. This analysis revealed a significant negative association between prenatal

marijuana exposure and FA and ND, as well as a positive association with MD and RD. These findings suggest that prenatal marijuana exposure is an independent predictor of disrupted WM integrity, even after accounting for sociodemographic differences. The observed changes in WM microstructure have important implications for cognitive and behavioral outcomes in exposed children. FA is a measure of directional water diffusion along axonal pathways and reflects WM integrity and neural connectivity. Lower FA values suggest reduced myelination or axonal degeneration [23], which can impair executive function, working memory, and processing speed. MD and RD are markers of myelin integrity, with increased MD values indicating higher axonal water diffusion and reduced cellular density, and increased RD values indicating impaired myelination or decreased axonal density [24]. Lastly, ND reflects the density of axons and dendrites in brain tissue [25]. The reduction in ND observed in children prenatally exposed to marijuana suggests fewer or less developed axonal projections, potentially disrupting connectivity between brain regions. Given that WM integrity supports higher-order cognitive functions, these structural changes may contribute to the increased risk of attention deficits, impulsivity, and executive dysfunction observed in children with prenatal marijuana exposure.

Recent studies have shown that dopamine plays a crucial role in the development of WM microstructure. PET imaging studies have demonstrated a relationship between dopaminergic activity and WM integrity, suggesting that dopamine receptor density is associated with fractional anisotropy in several key WM regions [26] . Prenatal marijuana exposure has been shown to reduce the dopamine D2 receptor expression in key brain regions involved in reward processing, through epigenetic modifications that may have long-term neurodevelopmental consequences [27]. Given the role of dopamine in WM development, these disruptions may contribute to the structural alterations observed in marijuana-exposed children. Furthermore, marijuana exposure has been linked to changes in dopamine-mediated behavioral phenotypes, including alterations in motivation and cognitive function [28]. Taken together, these findings suggest that prenatal marijuana exposure may have direct neurobiological effects on fetal brain development, rather than simply reflecting environmental or socioeconomic disparities.

Late childhood and early adolescence are important periods for the development of the brain WM microstructure [29-31]. Children prenatally exposed to marijuana in our study exhibited marked bilateral alterations in several WM tracts, many of which form part of the corticostriate circuitry, including the superior corticostriate tract and corticostriate projections via the external capsule to the superior parietal and frontal cortices. Prior studies have shown that prenatal marijuana exposure is linked to increased impulsivity and attention deficits in children [6]. These behavioral changes may be partially explained by disruptions in corticostriate WM pathways. The normal function of the corticostriate circuitry is essential for the development of goal directed behaviors. This includes the motivation and cognitive skills required to achieve specific goals [32]. Disruptions in this circuitry have been previously associated with psychiatric disorders such as stress induced depression and substance use disorders [33]. Children who are prenatally exposed to marijuana may therefore be at increased risk for developing challenges in goal directed behaviors and motivations. In addition, these alterations may potentially predispose these children to suffer from psychiatric disorders such as depression and substance use disorders later in life.

Cortical morphology alterations observed in children prenatally exposed to marijuana mirror our findings of WM microstructure disruptions. Reduced cortical surface was observed in the right hemisphere postcentral gyrus. The postcentral gyrus contains the primary somatosensory cortex and is responsible for the relay of somatic sensations throughout the body [34, 35]. In addition, recent studies have found that this brain region forms part of the human core empathy network [36]. Reduced development of cortical surface area due to prenatal marijuana exposure may lead to children experiencing impairments in sensory processing and empathic abilities, potentially affecting social interactions and emotional understanding. Reduced cortical surface area was also observed in the left hemisphere parahippocampal gyrus in those children prenatally exposed to marijuana. The parahippocampal gyrus is involved in the management of complex emotive process and is connected to many other components of the limbic system [37]. Decreases in the gray matter of this regions have been strongly associated with psychopathy [38]. Children prenatally exposed to marijuana, which experience marked reductions in this brain region may suffer from disrupted limbic system connectivity. Such alterations could potentially contribute to behavioral and emotional difficulties, including traits associated with psychopathy as they grow and develop.

The findings of this study align with previous research which analyzed the effect of prenatal exposure to marijuana on neonates. Studies have found that prenatal marijuana exposure is associated with altered striatal connectivity of neonates in areas associated with visuospatial and motor learning, attention regulation, and the refinement of motor outputs [39]. These findings align with our observed reduced WM microstructure in the striatal circuitry potentially indicating that the alterations caused by prenatal exposure to marijuana are already present at the early stages of neonatal neurodevelopment and may persist into late childhood. In addition, studies analyzing children ages 6 to 8 years found that those prenatally exposed to marijuana had alterations in brain cortical morphology, suggesting an alteration in proper neurodevelopmental maturation [8]. These findings also align with our results of delay cortical maturation in children prenatally exposed to marijuana at late childhood.

Our analysis of the ABCD dataset is the largest cohort study to date examining neuroimaging metrics alterations of brain neurodevelopment to assess the impact of prenatal marijuana exposure in late childhood. Our study extends existing knowledge by exploring the long-term effects of prenatal marijuana exposure on neurodevelopment into late childhood and early adolescence. By using the data of over 11,800 children who come from diverse socioeconomic, racial, and ethnic backgrounds we aim to enhance the generalizability of our findings. Furthermore, our study relies on the comprehensive analysis of multiple imaging modalities, studying both WM microstructural integrity and cortical surface area. This is different from previous studies, which typically rely on single imaging modality approaches, and allows for a more pervasive perspective on the long-lasting effects of prenatal marijuana exposure on children brain neurodevelopment.

While diffusion MRI remains primarily a research tool, advances in neuroimaging methodologies could enhance its utility in identifying WM alterations associated with prenatal marijuana exposure. Given that WM integrity is associated with cognitive and behavioral functions, neuroradiologists may have a role in recognizing these alterations in patterns, particularly in pediatric imaging. Although conventional MRI may not detect these microstructural changes, quantitative diffusion metrics such as FA and ND may serve as biomarkers for identifying children with neurological alterations. These imaging-based insights could eventually inform approaches to risk assessment

and long-term monitoring in children with prenatal exposure, though further study is needed.

Certain limitations should be considered when interpreting the findings of this study. First, our research utilizes data from the ABCD dataset, which collected data from 21 different sites across the United States. The ABCD study employs rigorous harmonization protocols to decrease site-related variability, including the use of standardized MRI acquisition protocols, centralized data processing pipelines, and comprehensive quality control procedures [40]. Additionally, structured demographic weighting methods have been applied to enhance sample representativeness and mitigate disparities related to socioeconomic status, race, and geographic location [18]. However, residual disparities in healthcare access, availability of community resources, and differences in local education systems may still influence neurodevelopmental outcomes in ways that are not fully accounted for. In addition, out of the original 11,868 participants, only 1,085 were included in our analysis due to incomplete demographic information or poor-quality brain imaging data. The cross-sectional nature of our study limits the ability to infer causality or track developmental changes over time. Significant associations identified in the analysis should not be interpreted as evidence of a causal relationship. Moreover, the ABCD study has no records of the pregnancy trimester of marijuana exposure, precluding more detailed analysis. Another limitation of this study is that we did not account for the potential effects of childhood trauma or adverse life events on brain development. Lastly, a limitation of this study is that we did not account for prenatal exposure to other substances, such as alcohol or tobacco. Given that prenatal substance use often involves polysubstance exposure, it is possible that some of the observed brain development alterations reflect combined effects rather than being solely attributable to marijuana exposure. Future studies should aim to examine the independent and interactive effects of multiple prenatal exposures on neurodevelopment. Despite these limitations, our study provides important insights into the long-term neurodevelopmental effects of prenatal marijuana exposure, contributing new valuable evidence on how prenatal marijuana exposure impacts neuroimaging metrics of brain health in late childhood.

CONCLUSIONS

Children who were prenatally exposed to marijuana showed notable brain neurodevelopmental alterations at a mean age of 9.9 years, as evidenced by our neuroimaging findings. Prenatal marijuana exposure was found to be associated with reduced WM microstructural integrity and delayed cortical development during late childhood. These alterations are predominantly observed in WM tracts and cortical regions essential for goal-directed behaviors, including motivation, cognitive skills for achieving specific objectives, and emotional processing. These findings remain significant even after controlling for factors such as race, ethnicity, parental income, education, and current BMI. Since the brain continues to mature through adolescence and early adulthood, it is important to monitor the development of children prenatally exposed to marijuana over time. Regular evaluations of their cognitive abilities, executive functions, and behavioral outcomes, in addition to early interventions, will be needed to understand and potentially mitigate the long-term effects of prenatal marijuana exposure.

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Tables

Table 1: Demographic characteristics of subjects included in the study

Characteristic	Complete Cohort before matching subjects (N = 7694)	Prenatal Marijuana Exposure (N = 418)	No Prenatal Marijuana Exposure Controls (N= 667)	P-values
Age at baseline, mean (SD), years	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	
BMI z score at time of scan, mean (SD)	0.35 (1.14)	0.73 (1.08)	0.70 (1.16)	0.646
K-SADS, number (%)	2140 (27.81)	152 (36.36)	240 (36.00)	0.950
Sleep Disorders	1067 (13.87)	75 (17.94)	110 (16.49)	0.592
Self-Injure/Suicidal Ideations	888 (11.54)	74 (17.70)	98 (14.69)	0.216
Bipolar Disorders	652 (8.47)	58 (13.88)	82 (12.29)	0.507
Depression	352 (4.57)	32 (7.66)	37 (5.55)	0.209
Anxiety	218 (2.83)	16 (3.83)	28 (4.20)	0.887
Sex, number (%)				0.125
Male	3832 (49.81)	196 (46.89)	346 (51.87)	
Female	3862 (50.19)	222 (53.11)	321 (48.13)	
Race and Ethnicity, number (%)				0.225
White	4492 (58.38)	174 (41.63)	286 (42.89)	
Black	956 (12.43)	121 (28.95)	155 (23.24)	
Asian	130 (1.69)	4 (0.95)	9 (1.35)	
Hispanic	1514 (19.68)	83 (19.86)	160 (23.99)	
Multiracial or Other	602 (7.82)	36 (8.61)	57 (8.55)	
Parental Education, number (%)				0.100
<High school	275 (3.57)	13 (3.11)	41 (6.15)	
High school or GED	606 (7.88)	59 (14.11)	109 (16.34)	
Some college	1928 (25.06)	195 (46.65)	272 (40.78)	
Bachelor's degree	2061 (26.79	79 (18.90)	124 (18.59)	
Postgraduate	2824 (36.70)	72 (17.22)	121 (18.14)	
Handedness, number (%)				0.745
Right	6194 (80.50)	324 (77.51)	528 (79.16)	
Left	533 (6.93)	30 (7.18)	48 (7.20)	
Mixed	967 (12.57)	64 (15.31)	91 (13.64)	
Family income, number (%)				0.431
<$5,000	252 (3.28)	19 (4.55)	56 (8.40)	
$5,000-11,999	252 (3.28)	38 (9.09)	54 (8.10)	
$12,000-$15,999	187 (2.43)	30 (7.18)	37 (5.55)	
$16,000-$24,999	340 (4.42)	34 (8.13)	64 (9.60)	
$25,000-$34,999	462 (6.00)	51 (12.20)	82 (12.30)	
$35,000-$49,999	643 (8.36)	56 (13.40)	77 (11.54)	
$50,000-$74,999	1038 (13.49)	60 (14.35)	100 (14.99)	
$75,000-$99,999	1145 (14.88)	48 (11.48)	80 (11.99)	
$100,000-$199,999	2442 (31.74)	63 (15.07)	92 (13.79)	
>=$200,000	933 (12.13)	19 (4.55)	25 (3.75)	

Footnote: Data are reported as mean (standard deviation), or number of subjects (percentage). BMI (Body Mass Index). K-SADS (Kiddie Schedule for Affective Disorders and Schizophrenia)

Figures

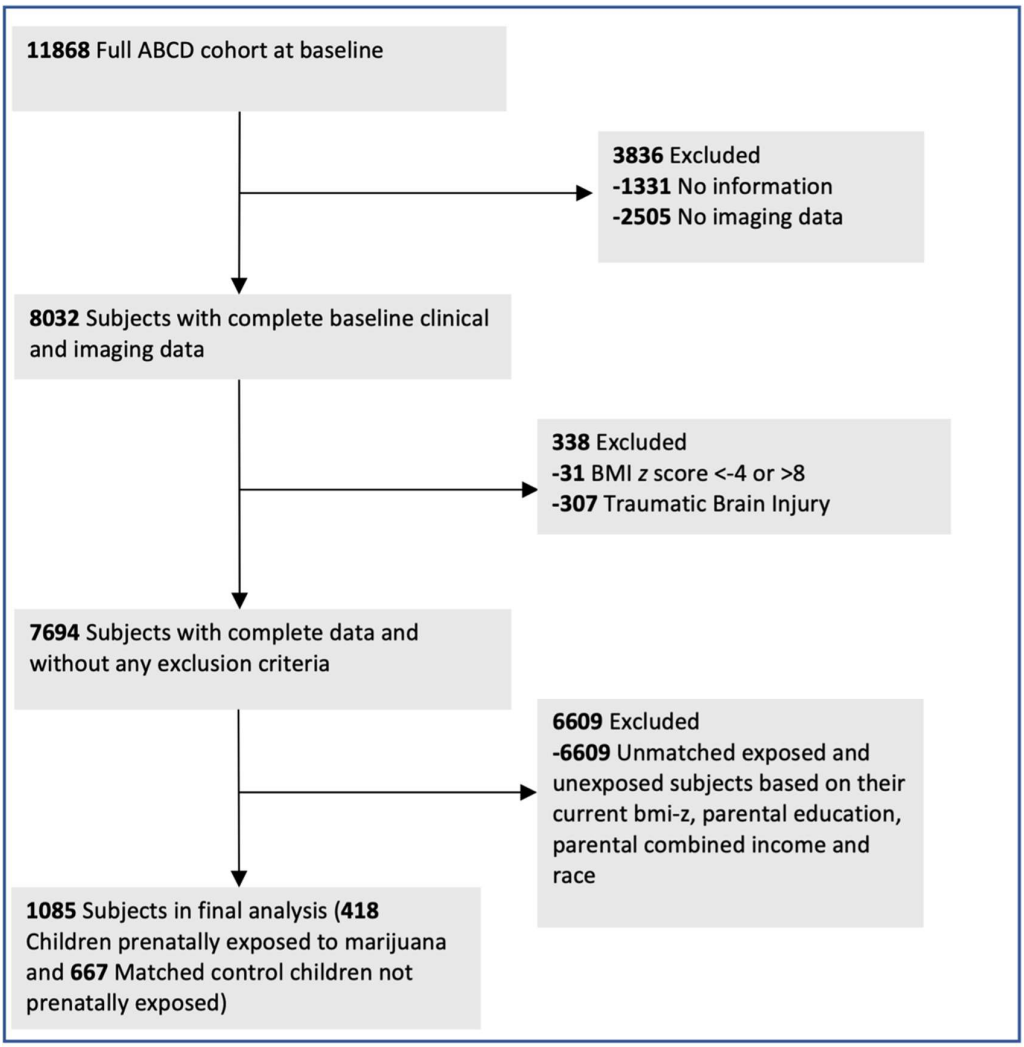

FIG 1. Flowchart depicting the inclusion of subjects for the analyses.

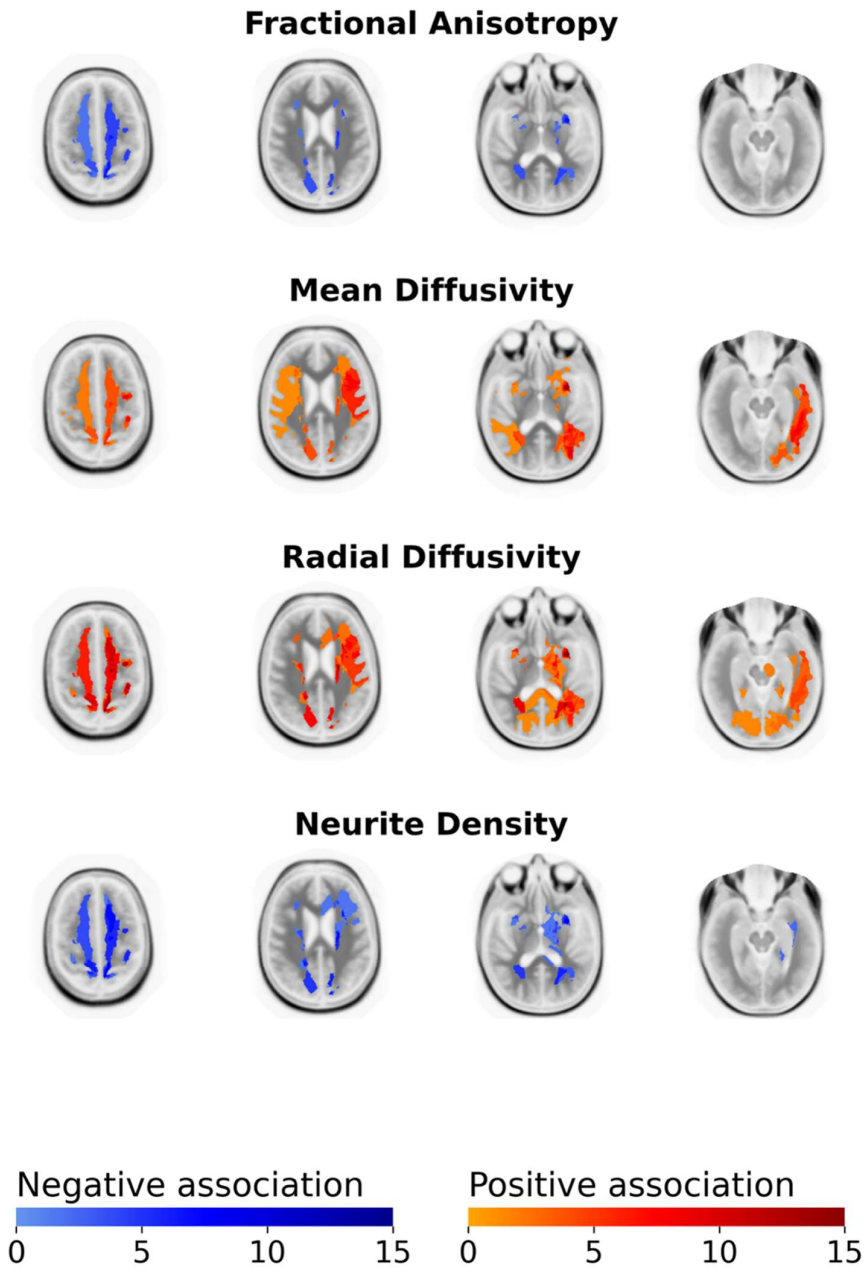

FIG 2. Mixed linear model analyses of the association of prenatal marijuana exposure with diffusion tensor imaging metrics. Values shown were corrected for subjects' age at time of imaging, sex, BMI z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects. Blue areas depict regions of significant negative association while red areas depict regions of significant positive association (both with false discovery rate corrected p-value<0.05).

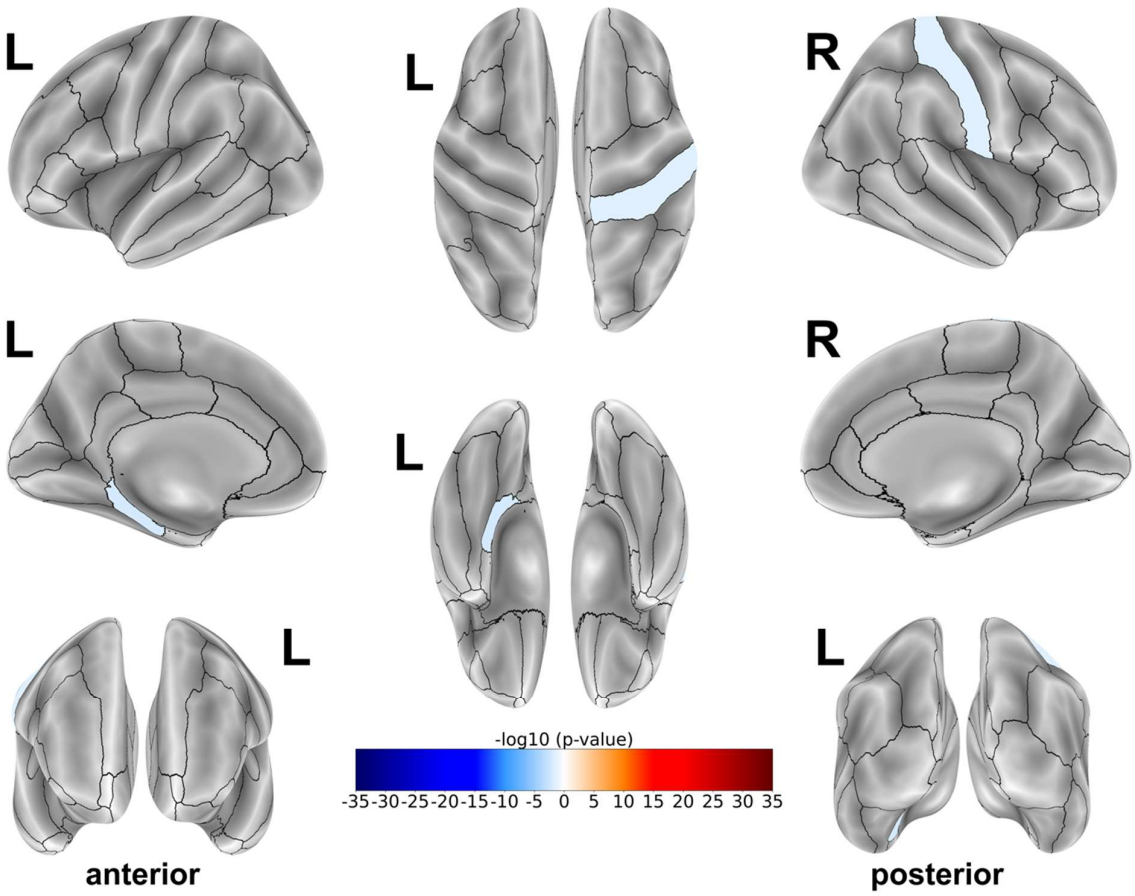

FIG 3. Mixed linear model analyses of the association of prenatal marijuana exposure with cortical surface area. Values shown were corrected for subjects' age at time of imaging, sex, BMI z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects. Blue areas depict regions of significant negative association while red areas depict regions of significant positive association (both false discovery rate corrected p-value<0.05). Note: All observed associations were negative, hence no red regions are present in the figure.

SUPPLEMENTAL FILES

Supplementary Table 1. List of all neuroimaging metrics analyzed in the study

Neuroimaging Modality	Imaging Metric
White Matter (DTI)	Corpus callosum
White Matter (DTI)	Forceps major
White Matter (DTI)	Forceps minor
White Matter (DTI)	Left and right fornix
White Matter (DTI)	Left and right cingulate cingulum
White Matter (DTI)	Left and right parahippocampal cingulum
White Matter (DTI)	Left and right corticospinal/pyramidal
White Matter (DTI)	Left and right anterior thalamic radiations
White Matter (DTI)	Left and right uncinate
White Matter (DTI)	Left and right inferior longitudinal fasciculus
White Matter (DTI)	Left and right inferior fronto-occipital fasciculus
White Matter (DTI)	Left and right superior longitudinal fasciculus
White Matter (DTI)	Left and right temporal superior longitudinal fasciculus
White Matter (DTI)	Left and right parietal superior longitudinal fasciculus
White Matter (DTI)	Left and right superior corticostriate
White Matter (DTI)	Left and right corticostriate projections via the external capsule to superior frontal cortex
White Matter (DTI)	Left and right corticostriate projections via the external capsule to superior parietal cortex
White Matter (DTI)	Left and right corticostriate projections to inferior frontal cortex
White Matter (DTI)	Left and right corticocortical projections from inferior frontal cortex to superior frontal cortex
Cortical Surface Area (sMRI)	Left and right banks of superior temporal sulcus
Cortical Surface Area (sMRI)	Left and right caudal anterior cingulate
Cortical Surface Area (sMRI)	Left and right caudal middle frontal
Cortical Surface Area (sMRI)	Left and right cuneus
Cortical Surface Area (sMRI)	Left and right entorhinal
Cortical Surface Area (sMRI)	Left and right fusiform
Cortical Surface Area (sMRI)	Left and right inferior parietal
Cortical Surface Area (sMRI)	Left and right inferior temporal
Cortical Surface Area (sMRI)	Left and right isthmus cingulate
Cortical Surface Area (sMRI)	Left and right lateral occipital
Cortical Surface Area (sMRI)	Left and right lateral orbitofrontal
Cortical Surface Area (sMRI)	Left and right lingual
Cortical Surface Area (sMRI)	Left and right medial orbitofrontal
Cortical Surface Area (sMRI)	Left and right middle temporal
Cortical Surface Area (sMRI)	Left and right parahippocampal
Cortical Surface Area (sMRI)	Left and right paracentral
Cortical Surface Area (sMRI)	Left and right pars opercularis
Cortical Surface Area (sMRI)	Left and right pars orbitalis
Cortical Surface Area (sMRI)	Left and right pars triangularis
Cortical Surface Area (sMRI)	Left and right pericalcarine
Cortical Surface Area (sMRI)	Left and right postcentral
Cortical Surface Area (sMRI)	Left and right posterior cingulate
Cortical Surface Area (sMRI)	Left and right precentral
Cortical Surface Area (sMRI)	Left and right precuneus
Cortical Surface Area (sMRI)	Left and right rostral anterior cingulate
Cortical Surface Area (sMRI)	Left and right rostral middle frontal
Cortical Surface Area (sMRI)	Left and right superior frontal
Cortical Surface Area (sMRI)	Left and right superior parietal
Cortical Surface Area (sMRI)	Left and right superior temporal
Cortical Surface Area (sMRI)	Left and right supramarginal
Cortical Surface Area (sMRI)	Left and right frontal pole
Cortical Surface Area (sMRI)	Left and right temporal pole
Cortical Surface Area (sMRI)	Left and right transverse temporal
Cortical Surface Area (sMRI)	Left and right insula

Supplementary Table 2. Two-Sample t-Test Analysis of Group Differences in Diffusion MRI and Cortical Morphology Metrics by Prenatal Marijuana Exposure Status

Imaging Metric	Mean Control Group	Mean Exposed Group	T value	Original p-value	Corrected p-value
Fractional Anisotropy - Left corticostriate projections via the external capsule to superior frontal cortex	4.41E-01	4.36E-01	-3.25E+00	1.21E-03	2.26E-02
Fractional Anisotropy - Left corticostriate projections via the external capsule to superior parietal cortex	4.72E-01	4.66E-01	-3.08E+00	2.17E-03	3.30E-02
Fractional Anisotropy - Left superior corticostriate	4.46E-01	4.40E-01	-3.43E+00	6.36E-04	1.54E-02
Fractional Anisotropy - Right corticostriate projections via the external capsule to superior parietal cortex	4.91E-01	4.85E-01	-2.93E+00	3.47E-03	4.22E-02
Fractional Anisotropy - Right superior corticostriate	4.71E-01	4.66E-01	-2.83E+00	4.69E-03	4.77E-02
Mean Diffusivity - Left superior longitudinal fasciculus	4.67E-01	4.70E-01	2.84E+00	4.58E-03	4.77E-02
Mean Diffusivity - Left temporal superior longitudinal fasciculus	4.67E-01	4.70E-01	2.82E+00	4.91E-03	4.77E-02
Neurite Density - Left anterior thalamic radiations	5.93E-01	5.88E-01	-2.94E+00	3.39E-03	4.22E-02
Neurite Density - Left corticostriate projections via the external capsule to superior frontal cortex	6.36E-01	6.31E-01	-3.54E+00	4.23E-04	1.29E-02
Neurite Density - Left corticostriate projections via the external capsule to superior parietal cortex	6.60E-01	6.55E-01	-3.64E+00	2.87E-04	9.96E-03
Neurite Density - Left fornix	5.11E-01	5.05E-01	-3.19E+00	1.47E-03	2.42E-02
Neurite Density - Left superior corticostriate	6.34E-01	6.29E-01	-3.98E+00	7.59E-05	4.67E-03
Neurite Density - Right corticostriate projections via the external capsule to superior parietal cortex	6.81E-01	6.75E-01	-3.48E+00	5.27E-04	1.42E-02
Neurite Density - Right superior corticostriate	6.60E-01	6.54E-01	-3.36E+00	8.11E-04	1.79E-02
Radial Diffusivity - Left anterior thalamic radiations	3.93E-01	3.96E-01	3.19E+00	1.49E-03	2.42E-02
Radial Diffusivity - Left corticostriate projections via the external capsule to superior frontal cortex	3.58E-01	3.62E-01	3.79E+00	1.64E-04	6.63E-03
Radial Diffusivity - Left corticostriate projections via the external capsule to superior parietal cortex	3.45E-01	3.49E-01	3.86E+00	1.23E-04	6.00E-03
Radial Diffusivity - Left parietal superior longitudinal fasciculus	3.41E-01	3.44E-01	2.90E+00	3.83E-03	4.43E-02
Radial Diffusivity - Left superior corticostriate	3.61E-01	3.65E-01	4.19E+00	3.11E-05	4.67E-03
Radial Diffusivity - Left superior longitudinal fasciculus	3.29E-01	3.33E-01	2.82E+00	4.91E-03	4.77E-02
Radial Diffusivity - Right corticostriate projections via the external capsule to superior frontal cortex	3.44E-01	3.47E-01	2.94E+00	3.41E-03	4.22E-02
Radial Diffusivity - Right corticostriate projections via the external capsule to superior parietal cortex	3.37E-01	3.41E-01	3.97E+00	7.69E-05	4.67E-03
Surface Area - Left Hemisphere Parahippocampal	6.80E+02	6.63E+02	-3.06E+00	2.31E-03	3.30E-02
Surface Area - Right Hemisphere Postcentral	4.31E+03	4.20E+03	-3.29E+00	1.06E-03	2.14E-02

Both the original and the false-discovery-rate-corrected p-values for multiple comparisons are provided. Only analyses with significant uncorrected p-values are included.

Supplementary Table 3. Mixed linear model analysis of the association of prenatal exposure to marijuana with fractional anisotropy (FA) values after controlling for subjects' age at time of imaging, sex, body mass index z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects.

White matter tract	Coefficient (95% confidence interval)	Original p-value	Corrected p-value
Left Fornix	-4.03E-03 (-8.03E-03 to -2.48E-05)	4.86E-02	1.35E-01
Left Corticospinal/pyramidal	-4.12E-03 (-7.62E-03 to -6.20E-04)	2.11E-02	6.56E-02
Left Anterior Thalamic Radiations	-4.23E-03 (-8.21E-03 to -2.53E-04)	3.71E-02	1.07E-01
Forceps Major	-5.01E-03 (-9.90E-03 to -1.13E-04)	4.49E-02	1.27E-01
Right Superior Corticostriate	-5.61E-03 (-9.58E-03 to -1.64E-03)	5.57E-03	1.98E-02
Left Superior Corticostriate	-5.24E-03 (-8.44E-03 to -2.05E-03)	1.30E-03	5.37E-03
Right Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	-4.41E-03 (-8.22E-03 to -6.11E-04)	2.29E-02	7.04E-02
Left Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	-4.89E-03 (-8.11E-03 to -1.67E-03)	2.89E-03	1.11E-02
Right Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	-6.07E-03 (-1.02E-02 to -1.96E-03)	3.81E-03	1.40E-02
Left Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	-5.54E-03 (-9.17E-03 to -1.92E-03)	2.72E-03	1.06E-02
Left Corticocortical Projections From Inferior Frontal Cortex To Superior Frontal Cortex	-3.35E-03 (-6.69E-03 to -5.77E-06)	4.96E-02	1.38E-01

Both the original and the false-discovery-rate-corrected p-values for multiple comparisons are provided. Only analyses with significant uncorrected p-values are included.

Supplementary Table 4. Mixed linear model analysis of the association of prenatal exposure to marijuana with mean diffusivity (MD) values after controlling for subjects' age at time of imaging, sex, body mass index z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects.

White matter tract	Coefficient (95% confidence interval)	Original p-value	Corrected p-value
Left Anterior Thalamic Radiations	2.82E-03 (3.37E-04 to 5.30E-03)	2.60E-02	7.89E-02
Right Inferior Longitudinal Fasiculus	3.02E-03 (5.46E-04 to 5.49E-03)	1.67E-02	5.38E-02
Left Inferior Longitudinal Fasiculus	3.65E-03 (1.29E-03 to 6.02E-03)	2.43E-03	9.59E-03
Right Inferior-fronto-occipital Fasiculus	2.69E-03 (2.37E-04 to 5.15E-03)	3.16E-02	9.36E-02
Left Inferior-fronto-occipital Fasiculus	3.46E-03 (1.06E-03 to 5.86E-03)	4.72E-03	1.70E-02
Right Superior Longitudinal Fasiculus	2.25E-03 (3.50E-04 to 4.16E-03)	2.03E-02	6.34E-02
Left Superior Longitudinal Fasiculus	3.06E-03 (1.09E-03 to 5.02E-03)	2.30E-03	9.18E-03
Left Temporal Superior Longitudinal Fasiculus	3.11E-03 (1.10E-03 to 5.12E-03)	2.38E-03	9.44E-03
Right Parietal Superior Longitudinal Fasiculus	2.36E-03 (4.62E-04 to 4.26E-03)	1.48E-02	4.85E-02
Left Parietal Superior Longitudinal Fasiculus	2.87E-03 (9.42E-04 to 4.80E-03)	3.53E-03	1.32E-02
Right Superior Corticostriate	2.61E-03 (8.98E-04 to 4.32E-03)	2.79E-03	1.08E-02
Left Superior Corticostriate	2.65E-03 (9.45E-04 to 4.36E-03)	2.32E-03	9.23E-03
Right Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	1.88E-03 (2.34E-04 to 3.53E-03)	2.52E-02	7.68E-02
Left Corticostriate Projections Via The External	2.50E-03 (8.14E-04 to 4.19E-03)	3.66E-03	1.37E-02

Capsule To Superior Frontal Cortex			
Right Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	2.71E-03 (9.01E-04 to 4.53E-03)	3.35E-03	1.26E-02
Left Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	2.77E-03 (9.42E-04 to 4.59E-03)	2.96E-03	1.14E-02
Left Corticocortical Projections From Inferior Frontal Cortex To Superior Frontal Cortex	1.92E-03 (2.05E-05 to 3.82E-03)	4.76E-02	1.32E-01

Both the original and the false-discovery-rate-corrected p-values for multiple comparisons are provided. Only analyses with significant uncorrected p-values are included.

Supplementary Table 5. Mixed linear model analysis of the association of prenatal exposure to marijuana with radial diffusivity (RD) values after controlling for subjects' age at time of imaging, sex, body mass index z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects.

White matter tract	Coefficient (95% confidence interval)	Original p-value	Corrected p-value
Right Fornix	2.97E-03 (8.52E-05 to 5.85E-03)	4.36E-02	1.24E-01
Left Fornix	4.21E-03 (1.34E-03 to 7.09E-03)	4.09E-03	1.49E-02
Left Corticospinal/pyramidal	2.83E-03 (9.54E-04 to 4.71E-03)	3.12E-03	1.19E-02
Left Anterior Thalamic Radiations	3.74E-03 (1.58E-03 to 5.91E-03)	7.15E-04	3.05E-03
Left Inferior Longitudinal Fasiculus	3.15E-03 (6.38E-04 to 5.65E-03)	1.39E-02	4.61E-02
Left Inferior-fronto-occipital Fasiculus	2.99E-03 (5.43E-04 to 5.44E-03)	1.66E-02	5.37E-02
Forceps Major	4.24E-03 (8.84E-04 to 7.59E-03)	1.33E-02	4.40E-02
Corpus Callosum	2.61E-03 (9.92E-05 to 5.11E-03)	4.16E-02	1.19E-01
Right Superior Longitudinal Fasiculus	2.31E-03 (1.00E-04 to 4.51E-03)	4.05E-02	1.16E-01
Left Superior Longitudinal Fasiculus	3.18E-03 (8.94E-04 to 5.46E-03)	6.39E-03	2.23E-02
Left Temporal Superior Longitudinal Fasiculus	3.13E-03 (7.99E-04 to 5.46E-03)	8.48E-03	2.89E-02
Right Parietal Superior Longitudinal Fasiculus	2.40E-03 (1.81E-04 to 4.62E-03)	3.41E-02	1.00E-01
Left Parietal Superior Longitudinal Fasiculus	3.27E-03 (9.92E-04 to 5.55E-03)	4.92E-03	1.76E-02
Right Superior Corticostriate	3.93E-03 (2.09E-03 to 5.77E-03)	2.83E-05	1.46E-04
Left Superior Corticostriate	3.79E-03 (2.13E-03 to 5.46E-03)	8.25E-06	4.47E-05
Right Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	2.93E-03 (1.18E-03 to 4.68E-03)	1.01E-03	4.21E-03
Left Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	3.52E-03 (1.83E-03 to 5.22E-03)	4.60E-05	2.26E-04
Right Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	4.15E-03 (2.18E-03 to 6.11E-03)	3.53E-05	1.80E-04
Left Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	3.91E-03 (2.04E-03 to 5.77E-03)	3.98E-05	1.99E-04
Left Corticocortical Projections From Inferior Frontal Cortex To Superior Frontal Cortex	2.57E-03 (4.06E-04 to 4.72E-03)	1.99E-02	6.23E-02

Both the original and the false-discovery-rate-corrected p-values for multiple comparisons are provided. Only analyses with significant uncorrected p-values are included.

Supplementary Table 6. Mixed linear model analysis of the association of prenatal exposure to marijuana with neurite density (ND) values after controlling for subjects' age at time of imaging, sex, body mass index z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects.

White matter tract	Coefficient (95% confidence interval)	Original p-value	Corrected p-value
Right Fornix	-4.33E-03 (-8.34E-03 to -3.19E-04)	3.43E-02	1.07E-01
Left Fornix	-5.75E-03 (-9.27E-03 to -2.23E-03)	1.36E-03	5.80E-03
Left Corticospinal/pyramidal	-2.74E-03 (-5.03E-03 to -4.55E-04)	1.88E-02	6.48E-02
Left Anterior Thalamic Radiations	-4.92E-03 (-8.42E-03 to -1.42E-03)	5.83E-03	2.27E-02
Left Superior Longitudinal Fasiculus	-3.70E-03 (-6.83E-03 to -5.83E-04)	2.00E-02	6.86E-02
Left Temporal Superior Longitudinal Fasiculus	-3.47E-03 (-6.59E-03 to -3.56E-04)	2.90E-02	9.22E-02
Left Parietal Superior Longitudinal Fasiculus	-4.10E-03 (-7.40E-03 to -8.02E-04)	1.48E-02	5.34E-02
Right Superior Corticostriate	-5.20E-03 (-8.31E-03 to -2.10E-03)	1.02E-03	4.63E-03
Left Superior Corticostriate	-5.05E-03 (-7.65E-03 to -2.45E-03)	1.40E-04	7.30E-04
Right Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	-4.08E-03 (-7.08E-03 to -1.07E-03)	7.78E-03	2.93E-02
Left Corticostriate Projections Via The External Capsule To Superior Frontal Cortex	-4.64E-03 (-7.35E-03 to -1.94E-03)	7.53E-04	3.52E-03
Right Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	-5.60E-03 (-8.77E-03 to -2.43E-03)	5.34E-04	2.59E-03
Left Corticostriate Projections Via The External Capsule To Superior Parietal Cortex	-5.26E-03 (-8.10E-03 to -2.41E-03)	2.92E-04	1.46E-03
Left Corticocortical Projections From Inferior Frontal Cortex To Superior Frontal Cortex	-3.39E-03 (-6.58E-03 to -1.91E-04)	3.78E-02	1.16E-01

Both the original and the false-discovery-rate-corrected p-values for multiple comparisons are provided. Only analyses with significant uncorrected p-values are included.

Supplementary Table 7. Mixed linear model analysis of the association of prenatal exposure to marijuana with cortical surface area values after controlling for subjects' age at time of imaging, sex, BMI z-score at time of imaging, handedness, race, and cranial volume at time of imaging as covariates and adjusting for the highest parental level of education and combined parental income level as random effects.

Region	Coefficient (95% confidence interval)	Original p-value	Corrected p-value
Lh-Banks Of Superior Temporal Sulcus	-2.48E+01 (-4.72E+01 to -2.33E+00)	3.05E-02	9.74E-02
Lh-lateraloccipital	8.49E+01 (1.20E+01 to 1.58E+02)	2.25E-02	7.51E-02
Lh-parahippocampal	-1.47E+01 (-2.38E+01 to -5.50E+00)	1.71E-03	7.21E-03
Rh-postcentral	-7.34E+01 (-1.30E+02 to -1.70E+01)	1.07E-02	3.92E-02

Both the original and the false-discovery-rate-corrected p-values for multiple comparisons are provided. Only analyses with significant uncorrected p-values are included.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1,2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	3,4
		(*b*) For matched studies, give matching criteria and the number of controls per case	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2,3
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	2,3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3,4
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	3
		(*d*) If applicable, explain how matching of cases and controls was addressed	2,3
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	8

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	4,5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
Generalisability	21	Discuss the generalisability (external validity) of the study results	4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.